34. (New claim) The composition as set forth in claim 1 wherein said carrier consists essentially of an antioxidant.

35. (New claim) The composition as set forth in claim 34 wherein said antioxidant consists essentially of an ascorbate.

36. (New claim) The composition as set forth in claim 34 wherein the antioxidant consists essentially of nordihydroguiaretic acid.

37. (New claim) The composition as set forth in claim 1 wherein the metal comprises a heavy metal.

38. (New claim) The composition as set forth in claim 1 wherein the metal is selected from the group consisting of copper, iron, manganese, molybdenum, and cobalt.

REMARKS

Claims 1-7 and 14-39 are pending in the application. Claims 8-13 have been cancelled. Claims 1-7 have been amended. Claims 34-39 are new claims.

Claim 1 is the sole independent claim in the application. Applicant's attorney observes that the amendment to claim 1 filed March 27, 2000 contained a clerical error in that it did not replicate unaffected portions of claim 1. Claim 1 as it appears with this response is the intended claim including the effects of the amendment filed March 27, 2000.

Claim 1 at lines 3-4 has been amended to recite the use of 8-hydroxyqunilone in an amount of at least 5% by weight, e.g., as supported on page 3 at lines 26-28 and other places in the specification. Claim 1 has also been amended to recite the use of an escharotic chelatable metal agent that is

present in a concentration less than an amount which produces an eschar (or chemical induced slough) in healthy mammalian tissues (lines 5-7). Support for these limitations may be found, for example, in the titration study that was performed using zinc chloride as the escharotic chelatable metal agent on page 17 at lines 7-20 of the specification, where a concentration of forty percent produced heightened redness proximate the lesion site and higher concentrations of 55% and 75% produced immediate escharotic effects. Amended claim 5 specifically recites use of up to the forty percent amount that specifically pertains to zinc chloride. Claim 1 at lines 9-10 has been amended to recite the use of 8-hyrdoxyquinoline and the metal chelating agent in a molar ratio ranging from 1:1 to 1:3, where support for this limitation may be found on page 3 at lines 24-26 of the specification. As is now recited in claim 1 at line6, support for the metal having a valence or oxidation state of +2 may be found, for example, on page 3 at lines 19-24 of the specification. The list of specific lesions (amended claim 1, lines 13-19) for which the composition demonstrates therapeutic utility is supported in the passage that runs from page 2 at line 29 to page 3 at line 16, and in the examples on pages 7-11 of the specification.

Various dependant claims have also been amended. Claim 2 has been amended to delete the former recitation of "effective amounts" for which antecedent basis has been deleted in claim 1. Claims 3 and 4 have been amended to depend from claim 1, as opposed to claim 2. Claim 4 has been amended to recite that the chelatable metal agent comprises zinc, and to delete reference to the absence of escharotic activity which is now recited in claim 1.

The use of zinc is supported, for example, on page 4 at lines 2-3 of the specification. Claim 5 has been amended to depend from claim 4, and to recite the use of zinc chloride in up to a forty percent amount, as is also supported by the titration study that is mentioned above. Claim 6 has been amended to reflect antecedents in the amended claim 1. Claim 7 has been amended to recite the composition in combination with necrotic tissue from the lesion of the claim 1 group, as caused by action of the composition. This type of necrotic tissue is, for example, mentioned on page 9 at lines 12-15 and other places in the specification, such as page 4 at lines 26-29.

Claims 14-22 have not been amended, but are replicated for the Examiner's convenience.

Claim 34 is a new claim that recites the "consists essentially of" use of an antioxidant, e.g., as described in Example 11 on pages 18-19 of the specification where sodium ascorbate (new claim 35) was used as the antioxidant and Example 4 on page 10 of the specification (new claim 36). See also page 4 at lines 15-21.

Claim 37 is a new claim that mentions the use of a heavy metal, as supported in the specification on page 4 at line 1. Specific metals including copper, iron, manganese, molybdenum and cobalt are disclose on page 4 at line 2 of the specification.

Claims 1-22 have been rejected under 35 U.S.C. §103(a) as being unpatentable over EP 0506207, which discloses that a zinc salt forms a chelate with 8-hydroxyquinoline in an equimolar or 1:1 ratio that is mixed with a carrier.

The use of zinc chloride in concentrations exceeding 35% (0.257 moles per 100g) is said to be avoided unless escharotic action is desired for purposes of decornification. "[L]ess than 35% zinc chloride should be considered an upper limit when no escharotic action is desired." See EP 0506,207 on page 3 at lines 24-34.

Amended claim 1 distinguishes EP 0506,207 by reciting the use of 8-hydroxyquinoline and the metal chelating agent each in amounts greater than five percent of the composition by weight. EP 0506,207 mentions the use of 8-hydroxyquinoline only in the context of an antifungal agent, and even then only in a laundry-list of other antifungual agents (EP 0506,207 on page 4 at lines 9-27). Despite generally language cited by the Examiner including the use of zinc chloride in an amount up to 35%, specific dosages for the antifungals are mentioned only in the most cursory terms including:

> The amount of the composition, and thus of the pharmacologically active agent therein to be administered, will obviously be an effective amount for the desired result expected therefrom. . . .Due to enhanced activity, which is achieved, the dosage of agent may often be decreased from that generally applicable." EP 0506,207 page 5 at lines 44-47.

The entire text of EP 0506,207 does not show that an antifungual composition including 8-hydroxyquinoline was ever actually made, or that a specific antifungal was ever mentioned. Other sources must be used to determine what dosage is "generally applicable," as taught by EP 0506,207.

The other document cited by the Examiner, GB 1,215,676 shows a variety of antifungual compositions including metal 8-quinolates. Page 1 shows a list of pure compositions, i.e., those having no carrier, which all have melting points

above 270°C. When a *carrier* is mixed with these compositions in a dosage for antifungual activity, the resultant composition includes only "one part by weight of at least one metal complex of 8-hydroxyquinoline." GB 1,215,676, page 1 at lines 15-17. The examples on pages 2-13 show that this amount is a maximum because the maximum concentration of a metal complex of 8-hydroxyquinoline is 1000 mcg/ml, or roughly 1% or less in these tables where the carrier is denser than water. This maximum of 1000 mcg occurs for nickel 8-quinolate on page 9 and iron 8-quinolate on page 10, with the remainder of concentrations in the tables being substantially less. Thus, the "generally applicable" antifungal dosage level that can be expected from the references is less than 1% by weight, whereas greater than 5% is presently claimed. Furthermore, as indicated above, EP 0506,207 teaches that this dosage may be *decreased* for antifungal activity due to synergy of the composition therein described.

It is apparent from the foregoing remarks that, considering the cited art as a whole, the documents teach that metal 8-hydroxyquinoline complexes are used for antifungal purposes and that the "generally applicable" antifungal dosages fall far below those which are presently claimed for use against the recited list of lesions. Specifically, claim 1 now recites that the 8-hydroxyquinoline and chelatable metal agent concentrations are each equal to or greater than 5% by weight.

The accompanying Declaration of Frank Potestio demonstrates the criticality of 8-hydroxyquinoline and zinc chloride each being present in amounts of at least five percent by weight. The criticality pertains to an effect that is

different in kind by virtue of eradicating the lesions that are identified in amended claim 1. Neither EP 0506,207 nor GB 1,215,676 recognize this criticality, as they have focused on use of metal 8-hydroxyquinolates for antifungal purposes in "generally applicable" dilute concentrations for antifugal purposes.

The EP 0506,207 reference is nonanalogous art with respect to the present claims because the document generally pertains to compositions having lower compositions demonstrating antifungal activity arising from generally lower concentrations than are presently claimed. These compositions having such lower concentrations are different in kind than the claimed composition, which demonstrates therapeutic affect for mammalian lesions. In support of the proposition that these documents are nonanalogous art, Applicant's attorney refers to the Examiner's own remarks in formulating the restriction requirement dated February 25, 2000, in which the Examiner stated on page 2, "the treatment of cancer is completely different than the treatment of warts." Therefore, the EP 0506,207, which insofar as it is relevant is merely directed to an antifungal composition including low-dosage 8-hydroxyquinoline, should not be applied against the amended claims.

Claims 1-22 have also been rejected under 35 U.S.C. §103(a) as being unpatentable over GB 1,215,676. Applicant's attorney requests clarification of the rejection because it does not appear that the GB 1,215,676 is combined with EP 0506,207 for purposes of formulating the rejection. Claim 1 distinguishes GB 1,215,676 is distinguished on the basis of dosage and nonanalogous art, as discussed above. The combination of documents, if such combination has been

made, is likewise distinguished for the same reasons that the individual documents are distinguished and because no suggestion has been made to combine the documents or to modify them individually.

The dependant claims have patentable merit in their own right, in addition to incorporating the limitations of the base claims from which they depend. Claim 2 specifically recites a molar ratio ranging from 1:1 to 1:3. EP 0506,207on page 3 at lines 24-34 teaches away from these features of claim 2 by reciting that the use of zinc chloride in excess of the 1:1 equimolar ratio should be exceeded only where escharotic activity is desired in the form of decornification and that the concentration of zinc chloride should then exceed 35% to provide an intended escharotic effect. Claim 2 distinguishes EP 0506,207 by reciting the use of zinc chloride (an escharotic metal chelating agent) beyond the 1:1 ratio, *but in amounts that do not have escharotic effects on healthy tissues.* Thus, EP 0506,207, in teaching that the equimolar ratio is to be exceeded only where escharotic decornification is desired, teaches away from the features of claim 2 where the ratio is exceeded without eschar formation and, consequently, there is no suggestion that EP 0506,207 can be modified for use against the present claims. Claim 3 recites the use of a 1:2 ratio. This ratio enhances the anti-lesion effects of the composition without requiring an excess of the escharotic chelatable metal agent. Claims 2 and 3 also distinguish GB 1,215,676 because GB 1,215,767 is limited to quinolates having a 1:1 ratio of metal to 8-hyroxyqunoline.

Claim 4 now recites the use of zinc as the chelatable metal agent. The Examiner notes on page 2 of the Office Action dated September 26, 2000, that the claims are still being examined as they read on zinc, however, a restriction to zinc is still improper when there is a generic linking claim, i.e., claim 1, that includes additional metals.

Claim 5 recites the specific forty percent zinc chloride weight identified by the titration study on page 17 of the specification, and claim 6 recites the five to twenty percent range. These ranges have effects that are different in kind, namely, the forty percent weight is a more powerful escharotic that produces redness adjacent the lesion, and the twenty percent weight normally is therapeutically effective without producing the associated redness. These features involving specific weights of zinc chloride could not have been predicted from the documents cited by the Examiner.

Claim 7 now recites the presence of necrotic lesion tissue in combination with the claimed composition. The use of the composition to treat the lesions specified in claim 1 could not have been predicted from the documents cited by the Examiner because those documents are only relevant to antifungals. Therefore, the claimed composition in combination with necrotic tissue from these lesions is novel and nonobvious.

The documents cited by the examiner are also silent as to the specific carriers that are recited in claims 14-15, the penetrants of claims 16-18, and the antioxidants of claims 19-21 and 34-36, all in combination with the composition of

claim 1, as well as the use of quercetin to provide the 8-hydroxyquinoline which is recited in claim 22.

Claims 1 and 22 have been rejected under 35 U.S.C. §112 because the claims fail to differ in scope. Claim 22 has been amended to recite the use of quercetin as a source of 8-hydroxyquinoline. Quercetin is an herb having high concentrations of 8-hyudroxyquinoline.

Claims 1-22 have been rejected under 35 U.S.C. §112 because the specification does not reasonably provide support for all cancerous lesions or precancerous lesions, but is merely enabling for those specific types of cancerous lesions or precancerous lesions that are disclosed. Applicants traverse and object to the statement that the specification lacks clear exemplary support for cancerous or precancerous lesions. These terms do read upon the various embodiments and therapeutic modalities that are disclosed. Furthermore, although the Examiner alleges that additional types of cancers could not be treated without undue experimentation using the disclosed instrumentalities, the fact remains that the disclosed instrumentalities have demonstrated therapeutic efficacy upon every single precancerous lesion or cancer to which the disclosed instrumentalities have been applied. Thus, we think that the breadth of claim is not "undue," nor is undue experimentation required to apply the disclosed compositions to a cancerous or precancerous lesion. Indeed, it is exceptional that a single composition of the type claimed demonstrates the disclosed spectrum of utility, and the showing of the application is one of breadth, as opposed to narrowness.

To address the Examiner's concerns in this regard, claim 1 now recites a specific list of the lesions that have been treated and are capable of being treated. Even so, the composition is being claimed and not the method of treatment. The list of lesions is recited only to buttress our argument that the claimed composition does in fact demonstrate therapeutic utility on lesions at least comprising that list, but utility against other lesions is not precluded. The claimed composition may demonstrate utility in a broader list of lesions in addition to those that are specifically recited.

The amended claims are patentable for the above reasons. No additional fees are seen to be due. However, if any additional fees are due, the Commissioner is authorized to charge them to deposit account No. 501324.

Respectfully submitted,
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